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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/455,683	05/31/95	BELL G	ARCD:177/WIM

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EXAMINER	
TENG, S	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

Office Action Summary	Application No. 08/455,683	Applica[illegible] Bell et al.
	Examiner Sally Teng	Group Art Unit 1646

☒ Responsive to communication(s) filed on *Jul 9, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *47-114* is/are pending in the application.

Of the above, claim(s) *53-58, 60-62, and 68-80* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *47-49, 51, 59, 63-67, 81, and 83-114* is/are rejected.

☒ Claim(s) *50, 52, and 82* is/are objected to.

☒ Claims *47-114* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Since this application is eligible for the transitional procedure of 37 CAR 1.129(a), and the fee set forth in 37 CAR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CAR 1.129(a). Applicant's first submission after final filed on July 9, 1999, has been entered.

2. Rejections that are not restated below are withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Acknowledgment is made of applicant's claim for foreign priority based on application PCT/US94/05747 filed on May 20, 1994. It is noted, however, that applicant has not filed a certified copy of the application as required by 35 U.S.C. 119(b).

Applicant has indicated that a substitute declaration will be filed to correct the priority claim of the present application. However, the Office has not received the substitute declaration.

4. Claims 47, 59, 63, 66, 84-91, 97, 103, and 109 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 47, 84, 91, and 97, it is not clear whether the claimed method is for screening a substance for its ability to interact with a kappa opioid receptor, since the steps seem to suggest

that a portion of the kappa opioid receptor be used in the assay. If the claimed method is to determine whether a test substance interacts with any opioid receptor, then it is not clear whether the results would be useful.

Claims 47 and 59 are vague and indefinite. Step(a) recites providing "an opioid receptor polypeptide selected from the group consisting of", but the alternative embodiments are groups of receptors. How many different chimeric opioid receptors or recombinant opioid receptors are provided for the assay? Also, it is suggested that either the term "opioid receptor polypeptide" or the term "opioid receptor" be used throughout the claim. Additionally, it is not clear whether the recombinant opioid receptor polypeptides are encoded by the same nucleic acid sequences.

Claims 59, 103, and 109 are confusing because it is not clear whether the claimed invention is directed to a method of isolating an agonist of a kappa opioid receptor. The method steps do not necessarily require a chimeric polypeptide comprising a kappa opioid receptor. Additionally, step (b) requires a composition but only recites one ingredient of the composition, the candidate substance. Is the receptor contacted with a composition or a single substance? It is also pointed out that "said candidate substance" lacks antecedent basis. Finally, the term "specifically interact" is vague and indefinite. The specification does not provide a definition for "specifically interact". It is not clear as to what interaction is considered a "specific interaction".

In claim 63, it is not clear whether the opioid receptor is the chimeric opioid receptor polypeptide of the recited alternative embodiments. Or does the claimed invention require an opioid receptor polypeptide that comprises a chimeric opioid receptor polypeptide?

In claim 66, "the polypeptide" lacks antecedent basis.

Claims 85-90 lack antecedent basis for "said polynucleotide".

5. Claims 47- 51, 59, 63, 66, 81, and 83-114 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The methods of claims 47 and 59 require providing an opioid receptor selected from the group consisting of (1) chimeric opioid receptors, (2) recombinant opioid receptors encoded by a nucleic acid comprising at least 30 contiguous bases of SEQ ID NO: 1, and (3) recombinant opioid receptors encoded by a nucleic acid comprising at least 30 contiguous bases of SEQ ID NO: 11. The claimed methods require exposing a test substance to a plurality of receptors, since the claims do not limit the receptors to one having a specific amino acid sequence or encoded by a specific nucleotide sequence. It would require undue experimentation of the skilled artisan to determine whether the test substance interacts with an opioid receptor because the test substance is incubated with a large number of polypeptides. In order to determine whether the test substance interacts with an opioid receptor, it is necessary to incubate the test substance with one opioid receptor at a time. Exposing the test substance to a mixture of chimeric opioid receptor polypeptides or a mixture of recombinant opioid receptor polypeptides makes it difficult to determine whether the test substance interacts with an opioid receptor.

The claimed methods use a broad genus of opioid receptor polypeptides for determining whether a substance interacts with an opioid receptor or acts as an agonist of a kappa opioid receptor. However, the specification teaches that the second extracellular loop of the kappa opioid receptor having the amino acid sequence as set forth in SEQ ID NO: 2 or 12 is required for ligand binding. The specification therefore only enables the use of a polypeptide comprising the second extracellular loop of kappa opioid receptor having SEQ ID NO: 2 or 12 for determining whether a substance interacts with or acts as an agonist of an opioid receptor. The claims as they stand do not require an opioid receptor polypeptide comprising at least the second extracellular loop of a kappa opioid receptor encoded by SEQ ID NO: 1 or 11. In fact, the claims as they stand do not even require that the polypeptide be functional. The claims encompass the use of any chimeric opioid receptor polypeptide or any recombinant polypeptide that is encoded by at least 30 contiguous nucleotides of SEQ ID NO: 1 or 11. The term "opioid receptor polypeptide" encompasses a polypeptide having a few amino acids, and 30 contiguous nucleotides only encode 10 amino acids. The specification does not teach whether 10 amino acids of SEQ ID NO: 2 or 12 are sufficient for ligand binding. The second extracellular loop of the mouse kappa opioid receptor has 61 amino acids. It is not predictable that 10 amino acids of the second extracellular loop of SEQ ID NO: 2 or 12 are sufficient for ligand binding. It is even more unpredictable that any 10 amino acids of a kappa opioid receptor are sufficient for binding. Thus, the specification does not enable the claimed method using the broad genus of opioid receptor polypeptides encompassed by the claims.

The claims also recite the use of a polypeptide encoded by a nucleic acid that is complementary to 30 contiguous nucleotides of SEQ ID NO: 1 or 11. It is pointed out that the complement of SEQ ID NO: 1 or 11 does not encode a kappa opioid receptor. The specification does not teach what the complement of SEQ ID NO: 1 or 11 encodes. Accordingly, it is not predictable as to what a nucleic acid that is complementary to 30 contiguous nucleotides of SEQ ID NO: 1 or 11 encode. It is not predictable that the encoded peptide can be used to determine whether a test substance interacts with an opioid receptor.

Additionally, the claims also recite the use of the polypeptide encoded by SEQ ID NO: 11 or peptides encoded by 30 contiguous nucleotides of SEQ ID NO: 11. However, SEQ ID NO: 11 is a nucleic acid sequence encoding a portion of the human kappa opioid receptor. It is not predictable that SEQ ID NO: 11 encodes a functional receptor. It is not predictable that SEQ ID NO: 11 encodes the second extracellular loop of the human kappa opioid receptor, which applicant has shown using the mouse kappa opioid receptor to be essential for ligand binding. Accordingly, without more information regarding the functional properties of the polypeptide encoded by SEQ ID NO: 11 or without the full length nucleic acid encoding human kappa opioid receptor, one would not be able to determine whether a substance interacts with an opioid receptor using the polypeptide encoded by SEQ ID NO: 11 or a peptide encoded by a portion of SEQ ID NO: 11.

Claims 47-52 and 81-102 are directed to a method of screening a substance for its ability to interact with any opioid receptor. It is not predictable that a substance that interacts with any

opioid receptor would be useful. If a substance interacts with a kappa opioid receptor, then it can serve as a ligand for a kappa opioid receptor. If a substance interacts with any opioid receptor, it is a non-specific ligand. In fact, it may interact with distantly related G-protein coupled receptor. Without knowledge as to which opioid receptors the ligand interacts with, the substance determined by the claimed method would not be useful as potential therapeutic agent or as a ligand in a binding assay. It is pointed out that some of the dependent claims seem to indicate that the claimed methods are directed to determining whether a test substance interacts with a specific chimeric opioid receptor polypeptide or a specific opioid receptor. However, the preamble as it stands is not directed to determining whether a substance interacts with a specific opioid receptor.

Claims 59, 103, and 109 and their dependent claims are not enabled for isolating an agonist of a kappa opioid receptor. The claimed method step do not require providing a chimeric polypeptide comprising the second extracellular loop of a kappa opioid receptor encoded by SEQ ID NO: 1 or 11 or a recombinant polypeptide encoded by SEQ ID NO: 1 or 11. If a functional second extracellular loop of a kappa opioid receptor encoded by SEQ ID NO: 1 or 11 is not used in the claimed method, then the skilled artisan would not be able to determine whether the test substance is an agonist for a kappa opioid receptor. The claimed method may show that the test substance is an agonist but since the kappa opioid receptor is not used in the method, it is not predictable that the substance is an agonist of a kappa opioid receptor. Moreover, it is pointed out that the assay does not enable distinguishing between agonists and antagonists. Both agonists and antagonists bind to the receptor. However, agonists mediate the functions of the receptor,

while the antagonists inhibit the functions of the receptor. Detecting the ability of a substance to bind to the receptor would only enable the skilled artisan to determine that the substance is a ligand. It is not predictable from the results that the ligand is an agonist or an antagonist. The claims are incomplete as method claims for determining that the substance is an agonist of a kappa opioid receptor.

Claims 59, 103, and 109 require contacting the opioid receptor polypeptide with a composition comprising said candidate substance. Although the claims are not clear as to what is present in the composition, it is pointed out that if more than one compound present in the composition is capable of binding to the receptor, then the claims would not be enabled by the specification. The claims do not include steps for distinguishing the candidate compound from other compounds that might bind to the receptor. Further, the composition may include compounds that interfere with the binding of the candidate compound to the receptor. Accordingly, the specification does not enable contacting an opioid receptor polypeptide with a composition comprising a candidate substance.

6. Claims 47, 59, and 84-114 are rejected under 35 U.S.C. 102(b) as being anticipated by Ahmed et al.

Ahmed discloses a method of screening for ligands that interact with the human kappa opioid receptor (page 862). The method of Ahmed comprises providing purified human kappa opioid receptor, incubating the purified receptor with labeled ligands, and detecting the binding of

the ligand to the kappa opioid receptor. Ahmed also performed competition assays to determine compounds that act as agonists of human kappa opioid receptor (pages 865-868). The competition assay comprises incubating purified human kappa opioid receptor with known agonists and labeled ligand and determining the IC_{50} of the binding of the receptor to the labeled ligands in the presence of known agonists. Thus, the claims are anticipated by Ahmed.

The rejection is maintained for the reasons set forth in the previous Office action and stated below.

Applicant's arguments filed July 9, 1999, have been fully considered but they are not persuasive.

Applicant argues that "isolating said substance if the ability of said substance to interact with the opioid receptor is detected". Ahmed teaches the claimed assays and shows the ligands that interact with the kappa opioid receptor. Ahmed has separated these ligands that interact with the kappa opioid receptor from those that do not interact with the human kappa opioid receptor. It is pointed out that the claims as they stand do not recite limitations for "isolation" or for "compositions comprising the candidate ligand" to distinguish from the assay taught by Ahmed.

Applicant urges that the claims recite the use of a chimeric opioid receptor or a recombinant opioid receptor polypeptide encoded by a nucleic acid sequence comprising at least 30 contiguous bases that are identical to SEQ ID NO: 1 or SEQ ID NO: 11. It is acknowledged that Ahmed does not disclose a chimeric opioid receptor. However, the claims recite the use of a recombinant polypeptide. A recombinant polypeptide is structurally or functionally the same as a

polypeptide isolated from its natural source, even though these two polypeptides are obtained by different methods. It is pointed out that a method used to obtain a polypeptide is not sufficient to distinguish it from the same polypeptide obtained by a different method. Additionally, all polypeptides are encoded by nucleic acids. The fact that Ahmed is silent as to the nucleic acid sequence encoding the polypeptide does not indicate that the polypeptide of Ahmed is not encoded by a nucleic acid. Applicant has provided no evidence that the polypeptide recited in the claims is different from the polypeptide of Ahmed. The burden is on the applicant to show that the disclosed human kappa opioid receptor is structurally and functionally distinct from the human kappa opioid receptor of the present claims (*In re Swinehart* 58 CCPA 1027, 439 F.2d 210, 169 USPQ 226 (1971)).

In re Deuel is not applicable to the present rejection. The present rejection is not based on using a partial amino acid sequence to obtain the full length nucleic acid sequence of a desired protein. The claims of the present application encompass the use of a human kappa opioid receptor and the prior art discloses the use of a human kappa opioid receptor. Although the prior art does not teach the nucleic acid encoding the receptor, this does not suggest that the human kappa opioid receptor of Ahmed is structurally and functionally distinct from the human kappa opioid receptor obtained by recombinant means cited in the claims.

It is reiterated that the present application is directed to the use of an opioid receptor polypeptide to screen for ligands that bind to the receptor. Unlike the copending application

08/147, 592, the present application is not directed to nucleic acids. The present claims do not require the use of nucleic acid, but polypeptide which is disclosed in the prior art.

7. Claims 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al. in view of Frielle et al.

Evans discloses a method of screening for ligands that interact with the delta opioid receptor (page 1953). The method of Evans comprises providing COS cells expressing the delta opioid receptor, incubating the COS cells with various labeled ligands, and detecting the binding of the ligand to the delta opioid receptor expressed on the surface of COS cells. Evans shows in figure 3 that the delta opioid receptor is a G-protein coupled receptor and is related to the well known somatostatin receptor. However, Evans does not disclose a method of screening for ligands that interact with chimeric delta opioid receptor.

Frielle teaches the use of chimeric β1/β2 adrenergic receptors in binding assays for determining the structure/function relationship of adrenergic receptors. In figure 2, Frielle shows that the chimeric adrenergic receptors of Frielle comprise a portion of the β1-adrenergic receptor linked to an alternate portion of the β2-adrenergic receptor. The results from the binding assay using the chimeric β-adrenergic receptor suggest that the different transmembrane regions may play a role in agonist and antagonist binding.

Since Frielle provides method steps for obtaining chimeric β-adrenergic receptor, and shows that chimeric β-adrenergic receptors, which are also G-protein coupled receptors, are

useful for ligand binding assays, the skilled artisan would have reasonably expected to successfully obtain chimeric delta opioid receptors wherein a portion of the delta opioid receptor is replaced by a closely related receptor, such as the well known somatostatin receptor (see Evans fig. 3) and to use the chimeric delta opioid receptors in ligand binding assays for obtaining ligands that interact with the chimeric delta opioid receptor. Accordingly, it would have been obvious to the skilled artisan at the time the invention was made to modify the ligand binding assay of Evans by using chimeric delta opioid receptor obtained by replacing a portion of the delta opioid receptor such as the seventh transmembrane domain and the following carboxyl terminus with that from the somatostatin receptor, as taught by Frielle in figure 2G for the chimeric β-adrenergic receptor, with the expectation of obtaining a chimeric opioid receptor that can be used in a ligand binding assay. The motivation to use chimeric delta opioid receptors in the ligand binding assay is that chimeric delta opioid receptors have different binding properties and would enable the skilled artisan to obtain more ligands that interact with opioid receptors. Thus, the claims are *prima facie* obvious over the prior art.

The rejection is maintained for the reasons set forth in the previous Office action and stated below.

Applicant's arguments filed July 7, 1999, have been fully considered but they are not persuasive.

It is acknowledged that neither Evans nor Frielle discloses chimeric opioid receptor. However, the cited references when taken together would suggest a chimeric opioid receptor

comprising a portion of the delta opioid receptor of Evans. *In re Rousselet* 146 USPQ 183 (CCPA 1965). In *In re Nilssen,* the court held that the cited references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen* 7 USPQ2d 1500 (Fed. Cir. 1988). Evans discloses the nucleic acid for the delta opioid receptor and shows that the delta opioid receptor is structurally related to somatostatin receptors. Frielle provides guidance for making chimeric adrenergic receptor for understanding the structure/function relation of adrenergic receptors. Accordingly, it would have been obvious to the skilled artisan to obtain chimeric receptors comprising the delta opioid receptor of Evans and the somatostatin receptor, by following the teachings of Frielle for use in binding assays to investigate the structure/function of opioid receptors. Although the adrenergic receptor of Frielle is not an opioid receptor, the adrenergic receptor of Frielle is related to the opioid receptors, since they are G-protein coupled receptors. The method of Frielle is applicable to making chimeric opioid receptors. Thus there is motivation to combine the cited references.

Applicant contends that there is no reasonable expectation of success in using chimeric opioid receptors in the claimed invention. Since the receptors of Frielle and the opioid receptor and the somatostatin receptor of Evans are all G-protein coupled receptors, the domains and loops of one receptor correspond to the domains and loops of the other receptor. Therefore, there is reasonable expectation of success in obtaining and using the chimeric opioid receptor in the claimed assay.

It is pointed out that the claims as they stand are not limited to chimeric opioid receptor having a specific amino acid sequence or containing a specific extracellular loop. The claims do not include the limitation that the chimeric opioid receptor comprises amino acid SEQ ID NO: 2 or 12. The claims encompass the use of a broad genus of chimeric opioid receptor polypeptides in the claimed assays. It is also pointed out that claims that are limited to chimeric opioid receptor having a specific amino acid sequence are not included under this rejection.

The present rejection is based on the teachings of the cited references and is not an improper "obvious to try" rejection. At the time the invention was made, it was well known to the skilled artisan, as demonstrated by the prior art, to obtain chimeric receptors to study the structure/function relationship of the receptor. Although it was not known as to what regions of an opioid receptor are essential for ligand binding, it was known that chimeric receptors can be made by substituting one portion of a receptor for a corresponding portion of a related receptor. It was also known that these chimeric receptors are useful in ligand binding assays.

8. Claims 50, 52, and 82 are objected as depending from a rejected base claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally Teng, Ph.D., whose telephone number is (703) 308-4230. The examiner can normally be reached on Mon.-Fri. from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310.

Official papers filed by fax should be directed to (703) 305-3014. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August 12, 1999

SALLY TENG
PRIMARY EXAMINER